

Aus dem Kinderspital Basel
(Chefarzt: Prof. Dr. med. Hottinger)

Renal Function Studies in Children
with Scarlet Fever Utilizing
the Addis Sedimentation Count
and the Volhard Concentration-dilution Test

Inaugural-Dissertation

zur Erlangung der Doktorwürde der Medizinischen Fakultät
der Universität Basel

vorgelegt

von

John A. Rein
von New York (U.S.A.)

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Prof. Dr. K. Bernhard
Dekan

RENAL FUNCTION STUDIES IN CHILDREN WITH SCARLET FEVER

The most feared complication of scarlet fever, before the introduction of Penicillin, was inflammation of the kidneys.

In 1936 Gram¹⁰ investigated the renal function in 14 cases of scarlatina from the initial stage of the exanthema. He intended to demonstrate changes in kidney function before the nephritis made itself clinically manifest. He estimated that 5 per cent of all scarlatina cases were complicated by hemorrhagic nephritis.

A study of 500 consecutive cases of scarlet fever, reviewed at the Basel Kinderspital from 1951 to 1956, revealed five cases, or 1 per cent, complicated by nephritis.

As a rule, nephritis is only slightly pronounced and unaccompanied by azotemia. However, degrees of severity range from very mild cases with transitory albuminuria and hematuria to the severest forms of uremia.

Today it is agreed that there exists no specific scarlatinal nephritis peculiar to this disease. When one speaks of scarlatinal nephritis, the „late nephritis“ is meant, that form appearing during the convalescent period most frequently at the end of the second or beginning of the third week. This is designated in the German literature „zweites kranksein“²¹.

Neu¹⁵ states that almost without exception the typical scarlatinal glomerulonephritis is an acute form. Two other forms of kidney disease are observed, but these, too, are not specific for scarlatinal nephritis¹⁶.

The diagnosis is arrived at only by continuous examination of the patient's urine. The most important symptomological manifestation of this inflammatory process in the kidney is hematuria, which, in the great majority of cases is recognized only microscopically.

The presence of all three urinary symptoms, hematuria, casts and albuminuria is practically never observed. Most frequently

one finds microhematuria of one or more days combined with a mild albuminuria. The hematuria in post infectious acute glomerulonephritis, in material studied by Neu¹⁵, presented mostly as microhematuria. Casts were nonexistent in the majority of cases, and edema, as a symptom, played a subordinate role.

Murphy's¹⁴ study of patients with chronic glomerulonephritis shows that in most cases a history of an acute attack is lacking. This observation is confirmed by Clausen⁵. Escaping recognition, the first evidence of renal damage appears months or years later with the development of the symptoms of chronic glomerulonephritis.

The severity of the initial attack is not a deciding factor with regard to the course and outcome of the disease. A mild, almost unrecognizable acute attack may gradually progress to the chronic phase. One must not assume that a clinical cure means that the lesion has healed. An interesting observation by Fishberg⁷ was that „possibly some of the cases of chronic glomerulonephritis date from scarlet fever in childhood“.

Addis¹ established the existence of a latent stage of nephritis, during which casts, red blood cells, epithelial cells and protein were excreted in abnormally large amounts for periods ranging from a month to twenty years. During this interval the patient remains in apparent good health and the ordinary tests of renal function indicate that the kidneys are normal. This latent stage of nephritis, with the complete absence of symptoms, together with the continuing excretion of blood cells, casts and protein, usually cannot be determined without the use of a special method of concentrating the urine.

Snoke⁷ points out that Addis was the first to offer proof that acute and chronic nephritis are, respectively, the beginning and the last stage of one continuing process.

This study has investigated renal function utilizing both the Addis sedimentation count and the Volhard concentration-dilution test. Twelve children suffering from scarlet fever were examined. The patients ranged in age from 2 to 9 years and were equally divided as to sex. All cases were treated with penicillin, the prescribed therapy at the Basle Kinderspital.

METHOD

Addis Count

Methods used for collecting specimens and making counts were those used by Lyttle¹³ for children. Fluids are restricted the day preceding the collection of urine. All urine passed between 8 P. M. and 8 A. M. is collected in one container. The volume, pH and specific gravity are determined. Ten cubic centimeters of this urine is pipetted into a graduated tube and centrifuged for ten minutes at 1800 revolutions per minute. 9.5 cc.'s of the supernatant fluid is removed and the remaining 0.5 cc. of sediment and urine is then mixed. One drop is removed and placed in an erythrocyte counting chamber. Casts, red blood cells, leucocytes and epithelial cells are counted in eight squares. The calculation is made using the following formula:

$$\frac{\begin{array}{l} \text{No. of casts} \\ \text{RBC's} \\ \text{WBC's} + \text{Ep.} \end{array} \text{ in 8 squares} \times 12 \text{ hour Volume} \times 1000}{16}$$

The normal limits are those suggested in Table I.

Table I

	Casts	RBC's	WBC's + Epithelial
Addis ²	(R) 0— 4,270	0—425,000	32,000—1,835,000
(Adults)	(A) 1,040	65,750	322,000
Lyttle ¹³	(R) 0—12,916	0—129,000	9,000—2,822,000
(Children)	(A) 1,085	15,181	322,484
Snoke ¹⁸	(R) 0—29,000	0—800,000	
(Children)	(A) 1,230	81,000	
Giles ⁹	(R) 0— 6,350	0—438,000	9,000— 714,000
(Children)	(A) 1,175	61,325	329,000
Proposed upper limits of normal in children	10,000	600,000	2,000,000

The above table illustrates the range (R) and average (A) counts of casts and cells in the urinary sediment of normal adults and children, and the proposed upper limits in children.

Table II

Volhard test			Addis count			
		Dilution	Concentration			
	Week	% excreted	specific gravity	specific gravity	RBC's	WBC's + Ep.
a)	2nd week	99	1.001	1.031	110,000	1,280,000
	3rd "	81	1.001	1.031	185,000	1,295,000
b)	2nd "	88	1.001	1.022	120,000	280,000
	3rd "	76	1.001	1.024	50,000	150,000
c)	2nd "	82	1.001	1.023	750,000	3,200,000
	3rd "	110	1.001	1.021	300,000	2,400,000
d)	2nd "	77	1.002	1.026	80,000	560,000
	3rd "	94	1.001	1.028	105,000	320,000
e)	2nd "	76	1.001	1.029	790,000	1,550,000
	3rd "	101	1.001	1.028	320,000	740,000
f)	2nd "	154	1.001	1.023	495,000	990,000
	3rd "	74	1.001	1.023	705,000	300,000
g)	2nd "	22	1.021	1.025	1,215,000	357,000
	3rd "	60	1.001	1.025	136,000	61,700
h)	2nd "	115	1.001	1.028	6,200,000	400,000
	2nd "				5,800,000	3,954,000
	3rd "	104	1.001	1.030	16,200,000	5,400,000
	4th "				2,712,500	3,363,500
i)	2nd "	105	1.001	1.029	88,000	177,000
	3rd "	91	1.001	1.028	105,000	800,000
j)	2nd "	109	1.001	1.030	1,008,000	4,592,000
	3rd "	78	1.001	1.027	820,000	2,450,000
k)	2nd "	70	1.001	1.030	105,000	210,000
	3rd "	92	1.001	1.029	140,000	280,000
l)	2nd "	107	1.001	1.033	125,000	50,000
	3rd "	22	1.001	1.025	40,000	162,000

Table II displays the results of the Volhard test and Addis count. The emphasized numbers represent those results which deviated from the norm. A graphic illustration of patient (h) is seen in Fig. I.

Volhard Concentration-Dilution Test

Fluid restrictions were enforced from the evening before the test until the beginning of the examination.

At 7 : 00 A. M. the patient voids and is then given water to drink in proportion to his weight. Urine is collected in separate containers at half hour intervals beginning at 8 : 00 A. M. and continued until

noon. All urine from 12:00 midnight until 8:00 A.M. the next morning is collected in one container.

The quantity and specific gravity of each sample is noted and plotted graphically. Normally the total quantity voided should be 80—120 per cent of the intake. The specific gravity of at least one specimen should be as low as 1.003.

For the evaluation of ability to concentrate, the urine is collected at two hour intervals beginning at 2:00 P.M. and continued until 8:00 P.M. The specific gravity and quantity are again measured and plotted. Normally, the specific gravity of at least one sample should be 1.030 or at least 1.025.

RESULTS

Reviewing the results of the Addis sedimentation study, six patients, four female and two male, are found to have elevated erythrocyte levels during the second or third weeks. Three of these children had corresponding elevations of the leucocyte and epithelial counts. In none of the patients studied were casts found. Cultures of the nasopharynx were positive for hemolytic streptococci in three of the children with abnormal urinary findings. During the second week of illness, at the time Addis count elevation occurred, patient (g's) progress was complicated by meningism and pyrexia. These figures are seen in Table II.

In only one case was an extreme increase in the Addis count observed. This occurred in patient (h) Table II. A graphic illustration is seen in Figure I. Studies were conducted periodically until the fourth week when the patient was discharged against the advice of the hospital staff. At this point the count was returning toward the upper limits of normal.

The results of the Volhard test reveal variations from the norm in nine of the patients. Decreased urinary excretion was found in eight of this group, but only one was combined with a high specific gravity, i. e. 1.021, in the dilution study. Deviations in ability to concentrate were found in three of the patients. Two children showed changes in both dilution and concentration examinations, and divergencies in both Addis and Volhard studies were found in five patients. An illustration of these results is seen in Figure II.

DISCUSSION

The results of the first Volhard examination in patient (g), Table II, revealing a diuresis of but 22 % of the fluid intake and the complete lack of dilution, may be explained on the basis of pyrexia and profuse perspiring observed at this time. It cannot be held accountable for the low (60 %) excretion during the second test. It must be understood that temperature elevation does not play a direct role in urinary concentration, only indirectly in relation to the volume excreted through the skin.

The poor results found in the dilution test of patient (1), Table II, may be explained on the basis of enuresis during the hours in which the test was in progress. Dilution is easily recognized, although the total diuresis was but 22 per cent.

There are a number of tests of kidney function, each group dependent upon certain physiologic principles. According to Belt³, the desiderata of a test of renal function may be summed up as follows:

1. It should be easy for the physician to apply and for the patient to carry out.
2. It should be easy to interpret.
3. It should be carried out through the agency of a nondeleterious substance, preferably one which the kidney is regularly called upon to deal.
4. The substance should be one which is not influenced by any other organ in the body.
5. The test should reveal slight impairment and yield an answer in per cent of normal, ranging uniformly through all changes, from slight impairment of function and structure to a total loss of kidney function.
6. It should reveal the nature of anatomic change occurring within the kidney.
7. The test applied in a chronologic series should have a prognostic value, indicating further degeneration or recovery.

No single test encompasses all of these criteria.

Dilution and concentration tests give the earliest warning of an impending failure of renal structure. The concentration tests serve

primarily for the purpose of determining the functional ability of the tubules.

The Addis count of urinary sediment is utilized to make the differentiation of the formed elements of the sediment of the urine more accurate.

Boyle, Aldrich, Frank and Borowsky⁴ investigated the usefulness of the Addis count in estimating the recovery of children from post-infectious nephritis. The count described by Addis¹ was based upon the idea that the type of renal pathology might be predicted from a study of the sedimentation. In 1926 he published what he considered to be normal figures for the various constituents².

It is not often possible to correlate the various tests which are supposed to express kidney function in per cent of normal. Readings taken at the same time in the same individual may be quite low in one type of test and definitely high in another. On the other hand, a very close correlation will be found to exist between different readings of the same test done on successive days. This discrepancy arises through the fact that each particular test must be an expression of a slightly different phase of kidney function. In order to give a graphic expression of these facts, Belt³ has compiled a chart which shows that the earliest sign of renal dysfunction is a fixation of specific gravity. This test is extremely sensitive in revealing slight damage, but it does not distinguish between a moderately advanced and a terminal stage of the disease. He states that an abnormal number of casts and red cells is the next most sensitive indication of disorder. This has a slightly quantitative significance when differential counts are compared from time to time. Attention is called to the fact that the urea clearance test has the widest range of all the tests attempted to express function in per cent of normal. It is not sensitive to changes less advanced than are represented by a loss of 20 per cent of the kidneys' functional capacity, but does permit readings on the low side of the scale all the way down to 5 per cent.

Furthermore, the phenolsulphonephthalein test is less sensitive to early changes than the urea clearance test. Zero readings are recorded by it when a wide margin of kidney function still exists.

The nonprotein nitrogen begins to be elevated as the phenolsulphonephthalein test approaches zero, and is always high when

the urea clearance test is 20 per cent or below. In the absence of general metabolic factors which might influence the degree of elevation of the nonprotein nitrogen, its level above normal marks the diminution of secreting tissue toward zero.

There is no need to discuss the remaining clearance methods since they give only partial information about the actual disease of the kidneys.

In the evaluation of the Volhard test, one must assume the existence of mild functional disturbance when the dilution is abnormal and the concentration does not reach 1.025. These findings take on importance when they are found to persist for several weeks or months. If the concentration is normal but the dilution abnormal, i. e. remaining above 1.004, it means that part of the water has been retained and is to be interpreted as a disturbance of extra-renal nature. If dilution and concentration persist during the entire test at or around 1.000, one can assume the existence of serious disturbance with renal function, possibly a prelude to a uremic state.

Results from the Volhard test done systematically during episodes of scarlet fever have revealed slight but transient disturbances of renal function. The results of Gautier's⁸ study, and those of this examiner, correlate closely.

The procurement of accurate samples of urine proves to be laborious at times, and this in turn leads to difficulty in assessing the results of the Volhard examination. This is confirmed in a study by Wohlleben²⁰. It is probably true to say that renal excretion tests in children are of less value than in adults because of the difficulties encountered in the collection of specimens.

The Addis count is only approximately accurate, and, unfortunately, in any urine many of the cells are so disintegrated that it is impossible to determine whether they were originally epithelial or white blood cells. A preponderance of epithelial cells exists in Degenerative Bright's Disease and a preponderance of erythrocytes in Hemorrhagic Bright's Disease⁵.

Aware of the confusing variations in size, shape and optical density of erythrocytes in the urinary sediment, a modified tissue stain, which appears to be specific for red blood cells, was described by Larcom and Carter¹¹.

A review of the results of the 12 children studied by means of the Addis count finds 50 per cent of these patients with abnormal sedimentation counts. The results described by Lyttle¹⁴ after performing the Addis count on 14 children who were recovering from scarlet fever found that all tests showed a moderate transient increase in the excretion of protein and formed elements during the period from the 8th to the 45th days after onset of the disease. In none was there the slightest clinical evidence of nephritis.

Giles'⁹ study of 218 cases of acute nephritis during a six year period with various excretion tests, demonstrated the raised red cell Addis count as the only indication that the renal lesion might still be active in 25 of these cases. This test, therefore, detects the presence of renal damage even when the blood pressure and non-protein nitrogen are normal and the renal function found to be unimpaired by the urea clearance and concentration tests.

Recovery should not be considered complete until the Addis count has been normal on numerous occasions for at least one year¹⁹. Giles⁹ expresses the belief that when the Addis count returns to normal and remains so on several examinations, the renal lesion has healed and a relapse is unlikely.

CONCLUSION

Consequently it is obvious that the Addis sediment count is valuable when the purpose is:

1) to detect latent nephritis; 2) to follow the transition from acute to chronic nephritis through the latent stage; 3) to detect the effects of therapeutic procedures or pharmaceuticals on the kidneys in health and disease; 4) to determine the incidence and duration of mild, clinically unrecognizable nephritis during the course or following acute infections; 5) to differentiate between true nephrosis and the nephrotic component of chronic glomerulonephritis. The two conditions can be distinguished in many instances only by repeated Addis counts.

The disadvantages are the time consumed in the procedure, the impracticability for office practice or even ordinary hospital or clinical work without a special technician devoting his full time.

Experience, nevertheless, has indicated that in many cases the information yielded justifies the added expenditure of time from the standpoint of both therapy and prognosis.

The Volhard and other concentration tests are capable of giving the earliest warning of the impending failure of renal structure because these tests determine the functional ability of the tubules. The test does not lend itself as well to the examination of small children as does the Addis count because of the difficulties encountered in the collection of urine samples. It should, however, be carried out when feasible.

The study has revealed that approximately 50 per cent of the scarlet fever cases which were examined have demonstrated injury to the kidneys of microscopic nature. The first indication of disturbance, revealed by the Addis count, occurred during the second week in five children. Only one child was found to have an abnormal count initially during the third week. The Volhard test indicates a similar result with five of the nine abnormal findings appearing initially during the second week.

With these results as a basis, the conclusion may be drawn that the third week of scarlatinal disease is not predestined for scarlatinal nephritis. Certainly before this period, definite signs of kidney involvement appear.

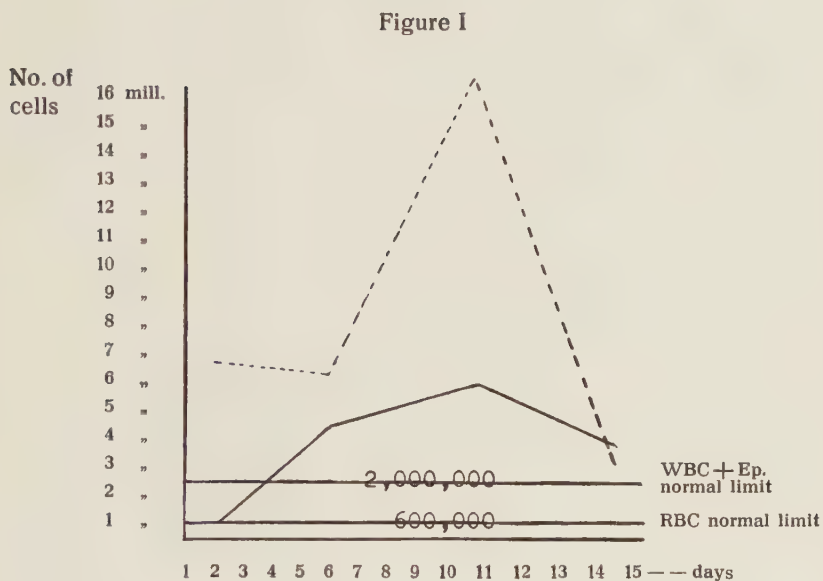
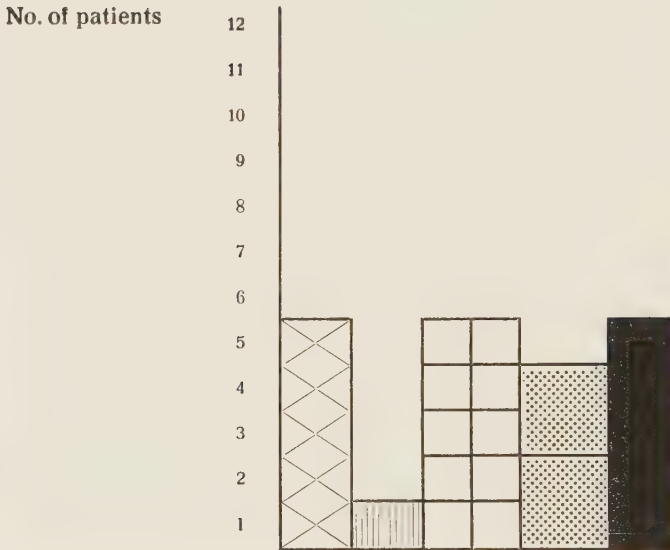


Figure I graphically illustrates the Addis count results of patient (h) Table II. The continuous line — represents the WBC+Ep cell count, and the interrupted line — — the erythrocyte count.

Figure II



Cases with abnormal Addis counts appearing initially during 2nd week.



Cases with abnormal Addis count appearing initially during 3rd week.



Cases with abnormal Volhard test appearing initially during 2nd week.



Cases with abnormal Volhard test appearing initially during 3rd week.



Cases with abnormalities in both Addis count and Volhard test.

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